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ORIGINAL ARTICLE

Laparoscopic colectomy for serosa-positive colon cancer (pT4a) in patients with preoperative diagnosis of cancer without serosal invasion

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Summary

Purpose: *Although general surgeons normally perform laparoscopic colectomies in patients with colon cancer, the procedure is also indicated for serosa-negative tumors (≤ cT3). Serosal invasion (T4a) is regarded as a potential risk factor for peritoneal dissemination due to pneumoperitoneum effects and tumor manipulation during laparoscopic colectomy. We compared short- and long-term outcomes of patients who underwent laparoscopic and open colectomies for serosa-involving colon cancer (pT4a) and had a preoperative diagnosis of cancer without serosal invasion (≤cT3).*

Methods: *A total of 179 patients (102 patients treated with laparoscopic colectomies and 77 with open colectomies) who were treated between 2009 and 2015 were included. These patients were first diagnosed preoperatively with ≤ cT3 disease based on computed tomography, endoscopy, or endoscopic ultrasound, but they were diagnosed with pT4a disease based on final pathology results. Recurrence and survival rates between the two groups were compared.*

Results: *Baseline characteristics, clinical stage, type of colectomy, and short-term outcome did not differ between the groups. Five-year overall survival (OS) (p=0.248) and disease-free survival (DFS) rates (p=0.113) were comparable between the laparoscopic and open groups. Recurrence patterns did not differ between groups. Moreover, laparoscopic colectomy did not increase peritoneal recurrence compared to open colectomy. By multivariate analysis, surgical approach was not an independent prognostic factor for OS or DFS.*

Conclusion: *Similar survival and recurrence patterns were observed in patients with serosa-involving colon cancer (pT4a) who were preoperatively diagnosed with serosa negative disease (≤cT3) and underwent either laparoscopic or open colectomies. Laparoscopic colectomy may be safely performed in patients with serosa-positive tumors.*

Key words: *colectomy, colorectal cancer, laparoscopy, minimally invasive surgery, serosal invasion*

Introduction

Laparoscopic colectomy has been accepted as an alternative treatment for selected patients with colon cancer based on long-term survival outcomes [1-5]. However, laparoscopic colectomy for cT4 colon cancer is not generally performed because of the risk of cancer cell dissemination resulting from laparoscopic tumor handling and pneumoperitoneum effects [6]. For this reason, laparoscopic colectomy performance is considered limited to ≤ cT3 disease [7]. However, to date, there has been no evidence regarding a higher incidence of peritoneal recurrence after laparoscopic colectomy for colon cancer compared to that which occurs after open colectomy. Although

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a few cases of port site recurrence have been reported, these do not appear to be clinically significant when compared to observations in many published reports [1-5].

Inevitably, as the number of laparoscopic colectomies performed for colon cancer increases, the number of patients who are pathologically diagnosed with pT4a will also increase [1-5], although the indication for laparoscopic colectomy is limited to ≤ cT3 cancers diagnosed using preoperative staging assessments [1-5]. This is because of the relatively low accuracy of preoperative diagnosis and inaccurate intraoperative evaluation [8-13]. There has been no report that focuses on the prognosis of patients who undergo laparoscopic colectomies for pT4a disease and who were preoperatively diagnosed with less advanced disease (≤ cT3). In this study, we investigated the short- and long-term outcomes of patients with pT4a disease that were preoperatively diagnosed with ≤ cT3 disease. Differences between groups treated using either laparoscopic or open colectomies were compared. Recurrence patterns, including peritoneal metastasis, were also analyzed.

Methods

This study complied with the Declaration of Helsinki and was approved by our local ethics committees. The need for informed consent from patients was waived because of the retrospective nature of this study.

From January 2009 to January 2015, a total of 179 patients who were diagnosed with T4a colon cancer that was previously classified as cT3 or less during the preoperative staging assessment via endoscopy, endoscopic ultrasound, or abdominopelvic computed tomography (CT) scan [14-17] were included in the study. Patients who underwent preoperative staging assessments without endoscopic ultrasound or who showed evidence of cT4a or more advanced disease that was suspicious for M1 disease were excluded from the study. Laparoscopic colectomy was indicated for tumors no more advanced than cT3 disease based on preoperative evaluation. All patients included in the study underwent R0 resections. Colon cancer stage was classified according to the 7th edition of the TNM classification of colon cancer, which was proposed by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) [18-23].

Of the 179 patients in the study, 102 were treated using laparoscopic colectomies, while the other 77 underwent open colectomies to treat colon cancer. All patients provided adequate preoperative informed consent after being given a full, detailed explanation of each surgical approach, including cost, advantages, and disadvantages. All patients decided the surgical approach they would receive. Laparoscopic colectomy has been described elsewhere in detail [24]. Open colectomies were performed similarly to laparoscopic colectomies, and patient management and follow-up were performed similarly in both groups. Postoperative complications occurring within 30 postoperative days were classified using the Clavien-Dindo classification. Major complications were classified as grades 3, 4, and 5. Minor complications were classified as grades 1 and 2 [25-38]. Patients diagnosed with stage II and III colon cancer after R0 resection were indicated for adjuvant chemotherapy and treated with a 5-fluorouracil (5-FU) based regimens [39,40].

Patients were seen in the outpatient department every 3 months for the first postoperative year, every 4–5 months for the next 2 years, and annually thereafter. Tumor recurrence was diagnosed using history, physical examination, endoscopic evaluation, radiologic investigations, or pathology when available. The patterns of recurrence were defined as follows: peritoneal recurrence and peritoneal seeding or Krukenberg tumor; distant recurrence: recurrence in the liver, lung, bone, brain, or distant lymph nodes; locoregional recurrence: recurrence in the colon, anastomosis, or regional lymph nodes; and mixed recurrence: multiple-site recurrence at the time of recurrence diagnosis.

Baseline data as well as short- and long-term outcomes were analyzed using medical records from a prospectively maintained colon cancer database. Patients were followed from the date of surgery until March 31, 2016 or death. OS was defined as the time from colectomy to death due to any cause. DFS was defined as the time from colectomy to disease recurrence or death due to any cause. OS and DFS were censored on March 31, 2016 if a patient remained alive.

Statistics

All statistical analyses were performed using SPSS 14.0 software (SPSS Inc., Chicago, IL, USA). For variables following normal distributions, data were presented as means and standard deviations and were analyzed by Student's *t*-test. For variables following non-normal distributions, data were expressed as medians and ranges and were compared by Mann-Whitney *U* test. Differences in semi-quantitative results were analyzed by Mann-Whitney *U* test. Differences in qualitative results were analyzed by chi-square test or Fisher's exact test where appropriate. Survival rates were analyzed using the Kaplan-Meier method, and differences between the two groups were analyzed by the log-rank test. Univariate analyses were performed to identify prognostic variables related to OS and DFS. Univariate variables with p values <0.10 were selected for inclusion in the multivariate Cox regression model.

Adjusted hazard ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. P values <0.05 were considered statistically significant.

Results

Baseline data are shown in Table 1. Among the 179 patients in the study, 102 and 77 underwent laparoscopic and open surgery, respectively. There were no differences in median age, clinical stage, or tumor location between the two groups.

Short-term outcomes are shown in Table 2. Conversion to open surgery was necessary in two patients undergoing laparoscopic colectomy because of massive adhesions. The median surgical time for the laparoscopic group was 210 min, which was significantly higher than the median of 170 min for the open group (p=0.029). Neither postoperative complication rate nor the severity of complications differed between the two groups. There was no postoperative 30-day death in either study group. Among all patients, 69 in the laparoscopic group and 57 in the open group completed adjuvant chemotherapy, while the remainder refused adjuvant chemotherapy or did not receive a complete course. However, no difference was found in adjuvant chemotherapy completion between the two groups.

Table 1. Comparison of baseline characteristics between the two groups

Characteristics	*Laparoscopic group (n=102) n (%)*	*Open group (n=77) n (%)*	*p value*
Age, years, median (range)	64 (45-71)	63 (41-74)	0.354
Gender			0.934
Male	47 (46.1)	35 (45.5)	
Female	55 (53.9)	42 (54.5)	
ASA score			0.818
I	82 (80.4)	63 (81.8)	
II	16 (15.7)	11 (14.3)	
III	4 (3.9)	3 (3.9)	
Clinical T stage			0.186
T1	8 (7.8)	4 (5.2)	
T2	25 (24.5)	14 (18.2)	
T3	69 (67.6)	59 (76.6)	
Clinical N stage			0.715
N0	69 (67.6)	54 (70.1)	
N1	34 (33.3)	14 (18.2)	
N2	4 (3.9)	9 (11.7)	
Tumor location			
Descending colon	20 (19.6)	13 (16.9)	0.642
Transverse colon	6 (5.9)	9 (11.7)	0.165
Ascending colon	49 (48.0)	38 (49.4)	0.862
Sigmoid colon	27 (26.5)	17 (22.1)	0.499

Pathologic outcomes are shown in Tables 3. There was no significant difference in pathologic outcomes between the two groups.

Table 2. Comparison of short-term outcomes between the two groups

Outcomes	*Laparoscopic group (n=102) n (%)*	*Open group (n=77) n (%)*	*p value*
Conversion	2 (2.0)	-	-
Type of resection			0.648
Right colectomy	21 (20.6)	18 (23.4)	
Extended right hemicolectomy	2 (2.0)	3 (3.9)	
Left colectomy	79 (77.5)	56 (72.7)	
Surgical time (min), median (range)	210 (180-320)	170 (170-320)	0.029
Blood loss (ml), median (range)	140 (120-320)	210 (160-420)	0.018
Patients with postoperative 30-day complications	11 (10.8)	10 (10.0)	0.633
Anastomotic leakage	1 (1.0)	2 (2.6)	0.805
Intra-abdominal abscess	3 (2.9)	4 (5.2)	0.713
Atelectasis	4 (3.9)	3 (3.9)	1.000
Wound infection	1 (1.0)	2 (2.6)	0.805
Ileus	3 (2.9)	2 (2.6)	1.000
Severity of complications			0.756
Major	2 (2.0)	1 (1.3)	
Minor	9 (8.8)	9 (11.7)	
Postoperative 30-day mortality	0 (0.0)	0 (0.0)	-
Adjuvant chemotherapy			0.273
Not received	10 (9.8)	3 (3.9)	
Incomplete	23 (22.5)	17 (22.1)	
Completed	69 (67.6)	57 (74.0)	

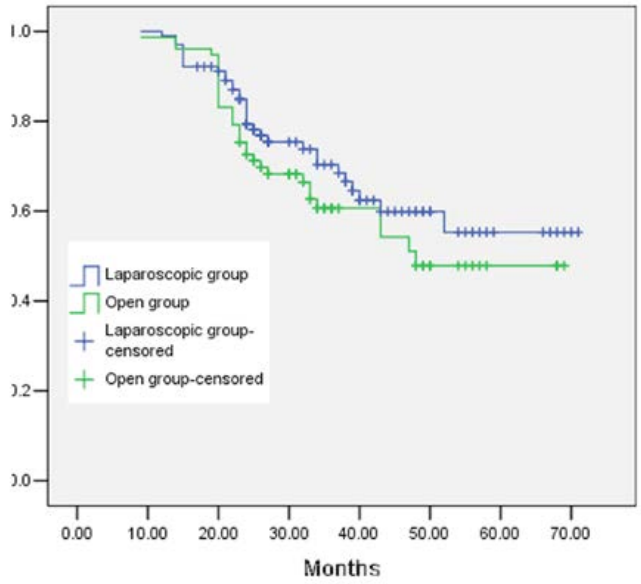

Figure 1. Kaplan-Meier overall survival curves for patients undergoing laparoscopic and open colectomy (p=0.248).

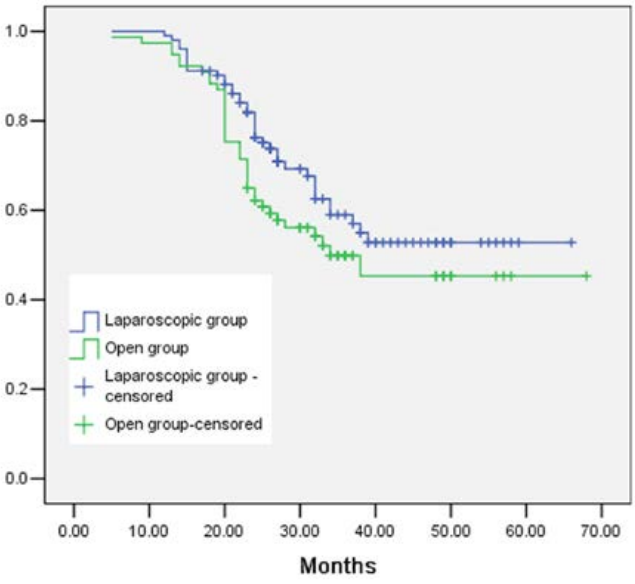

Figure 2. Kaplan-Meier disease-free survival curves for patients undergoing laparoscopic and open colectomy (p=0.113).

Table 3. Comparison of pathological data between the two groups

Pathological data	*Laparoscopic group (n=102) n (%)*	*Open group (n=77) n (%)*	*p value*
Histologic differentiation			0.181
Differentiated	58 (56.9)	36 (46.8)	
Undifferentiated	44 (44.3)	41 (53.2)	
Retrieved lymph nodes, n (range)	17 (15-29)	18 (15-28)	0.219
Pathological stage (pTNM)			0.568
II	42 (41.2)	35 (45.5)	
III	60 (58.8)	42 (54.5)	
Residual tumor			1.000
R0	102 (100.0)	77 (100.0)	
R1	0 (0.0)	0 (0.0)	
R2	0 (0.0)	0 (0.0)	

Table 4. Comparison of cancer recurrence data of the two groups

Outcomes	*Laparoscopic group (n=102) n (%)*	*Open group (n=77) n (%)*	*p value*
Tumor recurrence	37 (36.3)	33 (42.9)	0.147
Peritoneal recurrence	11 (10.8)	13 (16.9)	0.236
Locoregional recurrence	7 (6.9)	4 (5.2)	0.884
Distant metastasis	15 (14.7)	11 (14.3)	0.937
Mixed	4 (3.9)	5 (6.5)	0.664
Time to first recurrence, median (range, months)	22 (12-39)	17 (9-38)	0.091
Main treatment for cancer recurrence			
Metastasectomy	7 (6.9)	6 (7.8)	0.812
Chemotherapy	26 (25.5)	22 (28.6)	0.645
Supportive care	4 (3.9)	5 (6.5)	0.664

During the median follow-up period of 38 months, 37 patients in the laparoscopic group and 33 in the open group experienced tumor recurrence. The difference in recurrence rate was not statistically significant between groups (p=0.147). Death from cancer recurrence was noted in 35 of 37 patients who underwent laparoscopic surgery and in 31 of 33 who underwent open surgery.

There was no port site recurrence among patients who underwent laparoscopic surgery. The location of recurrence and time to first recurrence were not significantly different between the two groups (Table 4).

When OS and DFS were compared, no difference was found between the two groups. The 5-year OS rate was 58% in the laparoscopic group and 49% in the open group (p=0.248, Figure 1), and the DFS rates for these groups were 54% and 46%, respectively (p=0.113, Figure 2).

For all patients analyzed, the significant risk factors for poor OS were an undifferentiated tumor, no adjuvant chemotherapy, and higher pathologic N stage (Table 5). These three features were also significant risk factors for poor DFS. However, laparoscopic colectomy was not a risk factor for OS or DFS (Table 6).

Table 5. Multivariate Cox regression analysis of overall survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Histology			
Differentiated	1.00		
Undifferentiated	1.78	1.20-2.57	0.020
Adjuvant chemotherapy			
Completed	1.00		
Incomplete	1.24	0.87-1.55	0.097
No chemotherapy	2.89	1.59-2.99	0.011
Pathological N stage			
N_0	1.00		
N_1	1.28	0.77-1.41	0.158
N_2/N_3	2.88	2.11-4.48	0.005

Table 6. Multivariate Cox regression analysis of disease-free survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Histology			
Differentiated	1.00		
Undifferentiated	1.34	0.74-1.45	0.148
Adjuvant chemotherapy			
Completed	1.00		
Incomplete	1.24	0.87-1.55	0.200
No chemotherapy	2.89	1.59-3.99	0.037
Pathological N stage			
N_0	1.00		
N_1	1.22	0.54 -1.45	0.287
N_2/N_3	2.97	1.54-3.98	0.018

Discussion

In this study, OS and DFS were not related to the surgical approach used to treat the preoperatively underdiagnosed serosa-positive (pT4a) colon cancer. While surgical approach was not a prognostic factor, histologic type, adjuvant chemotherapy use, and pathologic N classification were prognostic factors for OS and DFS by multivariate analysis. In addition, the pattern of recurrence and the peritoneal recurrence rate after laparoscopic colectomy did not differ based on colectomy type.

Laparoscopic colectomy is an alternative treatment for colon cancer [1-5]. Prior evidence indicates similar long-term outcomes but better short-term outcomes for patients who undergo laparoscopic colectomies compared to those that undergo open colectomies [1-5]. However, laparoscopic colectomies are still only indicated to treat cT1–3 colon cancer because of the possibility of cancer cell dissemination to the peritoneal cavity and port sites [1-5]. Although many surgeons do not advocate performing laparoscopic colectomies for patients with T4 colon cancer, they often encounter some patients who were diagnosed with pT4 colon cancer after performing a laparoscopic colectomy because of inaccurate preoperative and intraoperative diagnoses [1-5]. Underdiagnosed patients like those in this study are regarded similarly to those who undergo open surgery. In this study, we found that laparoscopic colectomy was not a risk factor for poor prognosis and did not compromise long-term outcomes for patients who were originally underdiagnosed.

Recurrence rates in this study were 36.3% for the laparoscopic group and 42.9% for the open group, which are comparable to results obtained in previous studies. The 5-year OS and DFS rates for both groups were also similar to those previously reported [1-5]. Laparoscopic surgery did not relate to poorer OS or DFS, as seen in other studies [1-5]. According to our findings, the prognosis of patients who undergo open surgery seems to be worse than those who undergo laparoscopic colectomies, although the differences were not statistically significant. This is possibly because more aggressive cancers were included in the open surgery group, even after strict selection of patients to adjust for selection bias. Patient characteristics for each group were statistically comparable. However, there was more clinical subserosal and nodal involvement in patients with colon cancer included in the open group. Regarding recurrence patterns, our results show that selected T4a cancers treated using laparoscopic colectomy recur in similar patterns to cancers treated using open surgery, and laparoscopic colectomy performance did not increase peritoneal seeding or port site metastasis. This result was similar to those obtained in previous studies [1-5], which showed that using laparoscopic colectomy to treat colon cancer does not increase local, peritoneal, or port site recurrence.

Our study has some limitations. First, it was conducted on patients from a single institution, and it was performed retrospectively. Second, our study shows that only a limited number of patients with serosa-negative colon cancer according to preoperative and intraoperative diagnosis would be candidate for laparoscopic colectomy, although efforts should still be made to minimize direct handling of the tumor. Finally, our study enrolled a small number of patients. Thus, we may not have observed differences in survival due to the sample size. Therefore, a randomized clin-

ical trial with a larger sample size should be performed to confirm these results.

In conclusion, preoperatively underdiagnosed T4a colon cancer may be treated using laparoscopic colectomy without compromising long-term prognosis. This study provides baseline evidence for future randomized studies of laparoscopic colectomy to treat T4 colon cancer.

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Conflict of interests

The authors declare no confict of interests.

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